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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,331	06/19/2006	Orit Kollet	30694/41508	8331

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EXAMINER	
KIM, TAEYOON	

ART UNIT	PAPER NUMBER
1651	

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11/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,331	KOLLET ET AL.	
	Examiner	Art Unit	
	TAEYOON KIM	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-74* is/are pending in the application.

4a) Of the above claim(s) *11-35 and 47-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 7/23/2009 has been received and entered into the case.

Claims 1-10 are canceled, claims 11-35 and 47-74 have been withdrawn from consideration as being drawn to non-elected subject matter, and claims 36-46 are pending and have been considered on the merits. All arguments have been fully considered.

Claim Objections

The claim objection has been withdrawn due to the amendment.

Claim Rejections - 35 USC § 101

The claim rejection under 35 U.S.C.§101 has been withdrawn due to the cancellation of the rejected claims.

Claim Rejections - 35 USC § 102

The claim rejection under 35 U.S.C.§102 has been withdrawn due to the cancellation of the rejected claims.

Response to Arguments

Applicant's arguments filed 7/23/2009 have been fully considered but they are not persuasive.

Applicant alleged that Kollet et al. report that SCF induces CXCR4 expression, but does not teach or suggest isolating cells with increased CXCR4 levels for transplantation. This argument is not persuasive. As applicant indicated, the previous office action stated "Kollet discloses a method of isolating $CD34^{+}/CD38^{-}/CXCR4^{+}$ HSCs by flow cytometry (FACS) after treating $CD34^{+}/CD38^{-}$ or $CD34^{+}/CD38^{-/low}$ HSCs with SCF and IL-6 (see Materials and

Methods)." The HSCs of Kollet were cultured in the presence of SCF and IL-6, and SCF induces CXCR4 on HSCs. Thus, the method step of culturing HSC in the presence of SCF inherently results in the HSCs cells expressing CXCR4. Kollet clearly teach that the resulting isolated cell population is CXCR4 positive ($CD34^{+}/CD38^{-}/CXCR4^{+}$).

Even if this argument is based on the level of CXCR4 expressed in the cells for transplantation being above a predetermined threshold, the instant claims do not particularly disclose what would be the intended predetermined threshold level of CXCR4, and this limitation is interpreted to any level of increased expression of CXCR4 resulted from SCF treatment in these cells qualifies the limitation.

Since HSCs before and after incubation with SCF showed detectable differences in CXCR4 level, and the expression of CXCR4 is used as a selection marker to isolate CXCR4+ cells (see Fig. 2 of Kollet et al.), it is clearly a method step of isolating stem cells having CXCR4 levels above a predetermined threshold.

The claimed invention discloses the method steps comprising obtaining stem cells, exposing the stem cells to HGF along with SCF and IL-6, and isolating CXCR4 positive cells, and the cited references teach the limitation. Therefore, the intended results of generating stem cells suitable for transplantation would have been inherently carried out by the method steps of combined references.

Applicant also alleged that there is no synergistic effect when HGF is combined with SCF as taught by Weimar, and Weimar teaches that HGF alone failed to induce colony formation, while SCF increased the number of stem cell clusters. This argument is not persuasive. The rationale provided for the combination of HGF and SCF in the previous OA is

based on their similar, if not same, function of HGF and SCF beneficial to promoting cell proliferation, adhesion and cell survival, not because of any synergistic effect. Synergistic effect is not required to formulate obviousness rejection based on combining two components for the similar functions and/or purposes.

Even though HGF and SCF are not identical molecules, prior art (i.e. Weimar) teach that they have similar, if not same, effects on the stem cells. At the same time, a person of ordinary skill in the art would recognize that these molecules certainly possess different functions and/or properties. Unless such different function/property of HGF or SCF (e.g. different role in colony formation or having anti-fibrolytic function) prevents or teaches away to combine HGF and SCF, it would have been obvious to a person of ordinary skill in the art to combine these two molecules for the similar, if not the same, purpose.

With regard to the argument against the references cited that the combination of HGF and SCF based on the is not mere "duplication of parts" and requires "a new and unexpected result", a person of ordinary skill in the art do not need to produce "a new and unexpected result", which is a factor affecting to determining patentability (unobviousness), in determining obviousness based on the cited references. Applicant also asserted that the cited legal precedent (ie. In re Harza) does not apply for supporting combination of HGF and SCF, because it is not "mere duplication of parts". Even if In re Harza is considered not to support the rationale for combining two components for the same purpose, M.P.E.P. §2144.06 disclose "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re*

Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re* Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte* Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). This M.P.E.P. section has been added in the following claim rejection to clarify and support the rationale for combining HGF and SCF.

Applicant argued that one of skill would not be motivated to substitute HGF for SCF because these are different proteins with different functions yielding different effects. There is no indication or discussion in the previous OA in regard to the substitution of SCF with HGF, and the rejection did not state whether HGF can replace SCF. The rejection is based on the combination of HGF and SCF for the same purpose of promoting proliferation, cell adhesion and survival of the cited cells.

Based on the above discussion, the pending claim rejection should be maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kollet et al. (of record) in view of Weimar et al. (of record) in further view of Forbes et al. (of record), Devine et al. (of record) and Shi et al. (of record).

Kollet et al. teach a method of isolating $CD34^+/CD38^-/CXCR4^+$ HSCs by flow cytometry (FACS) after treating $CD34^+/CD38^-$ or $CD34^+/CD38^{-/low}$ HSCs with SCF and IL-6 (see Materials and Methods). Kollet et al. teach that CXCR4 mediates rapid and efficient homing of $CD34^+/CD38^-$ HSCs or $CD34^+/CD38^{-/low}$ HSCs (see whole document). Kollet et al. teach that SCF and IL-6 treatment, which increases CXCR4 expression, also increases migration and homing potential (p.3287, right col.), and suggest that the method provides a novel approach to improve the outcome of clinical stem cell transplantation by enhancing homing and repopulation with cytokines (p. 3290).

Kollet et al. do not teach the method step of exposing the stem cells to HGF.

Weimar et al. teach a method of exposing CD34+ hematopoietic stem cells (HSCs) to HGF.

It would have been obvious for the person of ordinary skill in the art at the time the invention was made to expose the stem cells of Kollet et al. to HGF as taught by Weimar et al.

The skilled artisan would have been motivated to make such a modification because Weimar et al. teach that HGF promotes proliferation, adhesion and survival of CD34+ HSCs (see whole document), and therefore, a person of ordinary skill in the art would recognize the benefit of HGF and would use the HGF for the preparation of HSCs suitable for transplantation.

Furthermore, Weimar et al. teach that SCF has a proliferative effect as well as adhesion effect similar to HGF (p.885-886). Since HGF has the same effect as SCF, it would have been

obvious to a person of ordinary skill in the art to combine HGF with SCF in the method of Kollet et al. to obtain promotion in proliferation, adhesion and survival of CD34+ HSCs.

It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04.

Furthermore, M.P.E.P. §2144.06 states "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re* Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte* Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

The person of ordinary skill in the art would have had a reasonable expectation of success in combining the step of exposing HSCs of Kollet et al. to HGF as taught by Weimar et al.

With regard to the limitations drawn to a method step of expressing HGF in the stem cells, Kollet et al. in view of Weimar et al. do not particularly teach the limitation. However, Forbes et al. teach that HGF as an antifibrotic agent being recombinantly expressed in bone-

marrow derived stem cells (p.2, lines 10-13; p.4, lines 18-26). It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the HGF-expressing stem cells of Forbes et al. in the method of Kollet et al. in view of Weimar et al. or modify the stem cells of Kollet et al. to express HGF as taught by Forbes et al.

The skilled artisan would have been motivated to make such a modification because since HGF is beneficial in proliferation, adhesion and survival of HSCs, using HSCs expressing HGF would eliminate an additional treatment step of HGF, since HGF secreted by the stem cells would act as an autocrine factor for the stem cells.

The person of ordinary skill in the art would have had a reasonable expectation of success in expressing HGF in HSCs since it is well known in the art to generate cells to express recombinant HGF by transfecting a polynucleotide encoding HGF.

With regard to the limitation of claim 37 drawn to the collecting step being effected by a stem cell mobilization procedure, Kollet et al. teach the stem cell mobilization procedure of stimulation with granulocyte colony-stimulating factor followed by obtaining such mobilized stem cells (see Materials and Methods).

With regard to the limitation of claim 46 drawn to a method step of determining homing capabilities of the CXCR4 expressing stem cells, Kollet et al. particularly teach the method step of analyzing homing capability of the stem cells expressing CXCR4 upon SCF and IL-6 stimulation (see "homing assay" in p.3284, right col.).

With regard to the limitation to the stem cells being mesenchymal stem cells, it would have been obvious to a person of ordinary skill in the art that the method of expressing HGF in the bone marrow derived stem cells of Forbes et al. would enclose HSCs as well as MSCs.

Therefore, by using the bone marrow-derived stem cells of Forbes et al. in the method of Kollet et al. would inherently carry out isolation of MSCs expressing CXCR4. Since it is well known in the art that MSCs have the homing property as HSCs according to Devine et al. (see whole document), and it is an inherent property of MSCs to express CXCR4 according to Shi et al. (see entire document), a person of ordinary skill in the art would have a reasonable expectation of success in isolating MSCs expressing CXCR4 along with HSCs in bone marrows in the method of Kollet et al. in view of Weimar et al. in further view of Forbes et al.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651